Prognostic relevance of cardiorespiratory fitness as assessed by submaximal exercise testing for all-cause mortality: a UK Biobank prospective study

Running Title: Prognostic relevance of CRF for all-cause mortality

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ABSTRACT

Objective: To investigate if the inverse associations of cardiorespiratory fitness (CRF) with all-cause and cardiovascular mortality in the general population vary among individuals who are at different pre-test risk.

Patients and Methods: CRF was assessed through submaximal bike tests in 58,892 participants aged 40-69 years who completed baseline questionnaires between January 1, 2006 and December 31, 2010 in the UK Biobank study. Participants were categorized into risk categories, which determined allocation to an individualized bike protocol. These were "minimal risk (1)", "small risk (2)" and "medium risk (3)" groups (i.e., those who cycled at 50%, 35% of predicted maximal workload and constant levels, respectively). We investigated associations of CRF with mortality across different levels of pre-test risk and determined whether CRF improves risk prediction.

Results: During a median follow-up of 5.8 years, 936 deaths occurred. CRF was linearly associated with mortality risk. Comparing extreme fifths of CRF, the multivariable adjusted hazard ratios (95% confidence intervals) for mortality were 0.63 (0.52-0.77), 0.54 (0.36-0.82), 0.81 (0.46-1.43) and 0.58 (0.48-0.69) in "minimal risk (1)", "small risk (2)" and "medium risk (3)" groups, and overall population, respectively. Addition of CRF to a 5-year mortality risk score containing established risk factors was associated with a C-index change (+0.0012; P=.49), integrated-discrimination-improvement (+0.0005; P<.001), net-reclassification-improvement (+0.0361; P=.005) and model difference (likelihood ratio test P<.001). Differences in 5-year survival were more pronounced across levels of age, smoking and sex.

Conclusion: CRF, assessed by submaximal exercise testing, improves mortality risk prediction beyond conventional risk factors and its prognostic relevance varies across cardiovascular risk levels.

Keywords: cardiorespiratory fitness; submaximal test; risk prediction; all-cause mortality; UK Biobank

Abbreviations

CI = confidence interval

CPX = cardiopulmonary exercise testing

CRF = cardiorespiratory fitness

CVD = cardiovascular disease

HR = hazard ratio

IDI = integrated-discrimination-improvement

IQR = interquartile range

MET = metabolic equivalent

NHS = National Health Service

NRI = net-reclassification-improvement

Introduction

Exercise testing with the assessment of cardiorespiratory fitness (CRF) is a procedure which may offer a wide prospect in risk assessment. Cardiopulmonary exercise testing (CPX) is considered to be the gold standard for assessing aerobic fitness; however, assessment of CRF using maximal CPX protocols with or without collection of respiratory gases is challenging in large population-based cohorts. Submaximal exercise testing is an easily available method used in measuring CRF and has been demonstrated to have good reliability and validity, with a good safety profile.[1, 2] There is a wealth of literature which shows CRF to be inversely and independently associated with vascular disease and mortality.[3-8] Limited evidence also suggests that CRF may provide additional prognostic value beyond established risk factors in predicting fatal vascular outcomes.[3, 9, 10] The inclusion of CRF in classic risk algorithms has been proposed, as it may improve the classification of an individuals' risk and optimize prevention.[11] However, its adoption as a vital risk assessment tool in clinical practice has been slow. The majority of risk prediction scores still rely on more traditional risk factors and do not consider CRF in their equation.[12, 13] Though several large-scale observational studies have evaluated the associations of CRF with the risk of mortality, most were either based on the general adult [14, 15] or highly select populations.[16, 17]

The relationships between CRF and mortality across different cardiovascular risk categories within the general population setting is not well known. In addition, the incremental prognostic information offered by the assessment of CRF in risk stratification beyond that of conventional risk factors in these risk groups has not been investigated in contemporary populations. The UK Biobank is a large, prospective, contemporary cohort study which add to the knowledge of CRF in risk prediction. This unique data which employs a safe submaximal exercise testing protocol provides an opportunity to clarify the

relationship between CRF and mortality in specific pre-test risk groups within the general population based on their level of engagement in exercise testing. Notably, the contemporaneity of this cohort compared to previous studies on CRF is relevant: as the treatment of cardiovascular risk factors and cardiovascular diseases (CVDs) have markedly changed in the last two decades, resulting in a reduction of cardiovascular mortality,[18] and the relationship and the prognostic relevance of CRF to overall mortality may also have changed. This study aimed to investigate the relevance of CRF on survival across different levels of cardiovascular risk and to assess whether information on CRF adds incremental value for the prediction of the risk for all-cause mortality beyond established traditional risk factors.

Patients and Methods

Study population

The UK Biobank study is a prospective cohort of middle-aged adult men and women recruited from 22 assessment centres across the UK. Approximately 9.2 million adults registered with the National Health Service (NHS) were initially contacted to participate in the study. Between January 1, 2006 and December 31, 2010, over 500,000 participants completed baseline questionnaires on prevalent morbidities, socio-demographic factors, family history, life-style and environmental factors; had their physical measurements taken; and provided biological samples.[19] From 2009, the study protocol was extended to include submaximal stationary bike tests to assess CRF. Prior to performing the bicycle test, study participants were grouped into one of five risk categories (based on their pre-test risk) namely: (i) "minimal risk"/category 1 (cycle at 50% level); (ii) "small risk"/category 2 (cycle at 35% level); (iii) "medium risk"/category 3 (cycle at constant level); (iv) "high risk"/category 4 (take measurement at rest-only); and (v) with no pre-defined category test (electrocardiography (ECG) to be avoided, either unsafe or pointless). Full details of exercise testing methodology have been described and justified in the UK Biobank Cardio Assessment protocol.[20] For the purposes of data completeness, we defined two

cohorts for the analysis. The first cohort ("*categories* cohort") which was mainly used for descriptive purposes, included participants for the analysis by a pre-defined category test: from the initial sample of 95,153 participants, 17,197 were excluded because they did not fit for any pre-defined category due to their clinical status (**Supplementary Table S1**), leaving 77,956 individuals in the 4 risk categories (categories 1 to 4). From this sample, 1,655 were further excluded due to missing data on one or more covariates, leaving 76,301 participants for the analysis (**Supplementary Table S2**). The second cohort ("*fitness* cohort") which was used for the main analyses, included 59,763 participants in exercise test categories 1, 2, and 3 after exclusion of 6,298 participants for not being able to complete the bicycle test; 8,245 for having at-rest measurements (category 4); and 3,650 with missing data on variables for estimating CRF (**Supplementary Table S3**). On further exclusion of participants with missing data on one or more covariates, there remained 58,892 participants for the analysis (**Supplementary Table S4**). For both cohorts, less than 1% of data was missing for covariates.

Assessment of CRF

Cardiorespiratory fitness was assessed using a 6-min incremental stationary bicycle ergometer protocol (eBike Comfort Ergometer, General Electric, firmware version 1.7) submaximal test with workload calculated according to age, height, weight, resting heart rate, and sex. The heart rate was monitored before the exercise protocol, throughout the exercise test and during recovery via a four-lead ECG. As described above, the participants were categorized into risk groups which enabled assignment to an individualized bike protocol and was done to increase the number of participants with exposure information and reduce the risk of adverse health events during exercise testing. The participants' predicted maximum workload was calculated using the formula based on age, sex, weight, height and resting hear rate.[20] Participants in the "minimal risk" and "small risk" categories underwent standard bike protocols, which comprised of (i) an initial 15-s seated-rest period; (ii) a 2-min phase at constant

power (30 watts for women; 40 watts for men), (iii) a 4-min ramp phase with linear increases in power from their initial constant power to their individually assigned peak power (to 50% and 35% of predicted maximal workload for 'minimal' and 'small' risk, respectively), and (iv) a 1-min recovery period. Participants in the "medium risk" category cycled at the constant power level for 6 min; they were asked to cycle at 60 revolutions-per-minute during all cycling phases. Participants in the 'high' risk category, who only did a 2-min seated-rest assessment and those 'ineligible' for ECG testing were excluded from the analysis.

Heart rate data collected during the test were used to calculate CRF using an approach that has been described in previous reports.[15, 21, 22] Briefly, the work rate at maximal heart rate was estimated by extrapolating the pre-exercise heart rate and the heart rate and work rate at the end of the test, to the age-predicted maximal heart rate (208–0.7 × age)[23] assuming a linear relationship. Maximal oxygen uptake (i.e. at maximal heart rate) was estimated from the regression equation for the relationship between work rate and oxygen uptake [oxygen uptake (in mL kg^{-1} min^{-1}) = 7 + (10.8 × work rate (W))/body mass (kg)], which was then expressed in terms of maximal metabolic equivalents (METs) (where 1 MET = 3.5 mL kg^{-1} min^{-1}).

Ascertainment of covariates

Age was calculated from dates of birth and date of baseline assessment. Medical history (including cancer, CVD and diabetes) and lifestyle characteristics were collected from the self-completed, baseline assessment questionnaires. Smoking status was categorized into never, former, and current smoking. Height and body weight were measured by trained nurses during the baseline assessment visit. Body mass index (BMI) was calculated as weight [kg] / height $[m]^2$). Detailed description of assessment of confounders have been provided in the UK Biobank online protocol.[24]

Outcome ascertainment

Our outcome of interest was all-cause mortality. Mortality status was ascertained by linking Biobank data with death records from the NHS Information Centre (England and Wales) and the Scottish Morbidity Record (full details of linkage procedures are available online.[24] Participants were followed-up between study entry until date of death or date of censoring: 31 January 2016 for England and Wales; 30 November 2015 for Scotland. Deaths due to CVD and deaths due to cancer were identified on the basis of the International Classification of Diseases-10 codes I00-I79 and C00-C97, respectively.

Statistical analyses

Baseline characteristics of study participants were summarised using descriptive statistics. Flexible parametric proportional hazard survival models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for all-cause mortality. Model-based 5-year standardized (adjusted) survival estimates were also computed.[25] To assess shapes of the associations between CRF and mortality risk in each risk group, HRs were calculated within fifths of baseline CRF and plotted against mean CRF levels within each fifth. Floating variances were used to calculate 95% CIs for the log HR in each group (including the reference group, first fifth/lowest CRF), to allow for comparisons across the groups irrespective of the arbitrarily chosen reference category. Hazard ratios were adjusted for age, sex, systolic blood pressure (SBP), BMI (nonlinear spline with 5 knots at equally spaced centiles of the distribution), smoking status, high cholesterol, number of medications, and history of cancer, CVD, or diabetes mellitus. Effect modification by individual characteristics, such as age, sex, and other cardiovascular risk markers were assessed using interaction tests. To assess whether adding information on CRF to established risk factors is associated with improvement in prediction of mortality risk, we calculated measures of discrimination for censored time-to-event data using Harrell's C-index[26] and

reclassification.[27, 28] To investigate the change in C-index on the addition of CRF, two mortality risk prediction models were fitted: one model based on traditional risk factors which are commonly used in European CVD risk scores (i.e., age, sex, SBP, smoking, and cholesterol[12]) and the second model with these risk factors plus CRF. Reclassification analysis was restricted to the first 5 years of follow-up because of the follow-up time accrued for the Biobank study and was assessed using the net-reclassification-improvement (NRI)[27, 28] and integrated-discrimination-improvement (IDI)[27] by comparing the model containing conventional risk factors to the predicted risk from the model containing conventional risk factors plus CRF. Reclassification analysis was based on predicted 5-year mortality risk categories of >2.5%; 2.5 to 3.75%; 3.75 to 5.0%; and >5.0% as previously reported for 5-year follow-up.[29] Given that Harrell's C-index is based on ranks rather than on continuous data, it can be insensitive in detecting differences.[30, 31] To avoid discarding potential biomarkers that can be used in risk prediction, we complemented the above indices with several others (eg, likelihood ratio test, R^2, Akaike and Bayesian information criterion), which have been recently suggested to be more sensitive when evaluating the added predictive value of a new measurement.[32] Importantly, these indices facilitate the assessment of the prognostic relevance of CRF across patient-level characteristics. In a sensitivity analysis, we further excluded participants with baseline cancer or CVD from the *fitness* cohort. All statistical analyses were conducted using Stata version 15.1 (Stata Corp, College Station, Texas, USA).

Results

Baseline characteristics and associations

Baseline characteristics of individuals according to the 4 pre-test risk categories ("*categories* cohort") are reported in **Supplementary Table S5**. Model-based 5-year standardized survival curves demonstrated a lower risk of death among individuals who cycled at 50% level (category 1) (**Figure 1)**. Comparing individuals in category 4 with those in the category 1, the HR (95% CIs) for mortality was

1.63 (1.41 to 1.88) (**Supplementary Table S6**). Characteristics of participants of the "*fitness* cohort", overall and by risk categories, are summarised in **Table 1**. The overall median (interquartile range, IQR) age at baseline was 58.1 (50.2-63.6) years and there were 28,319 (48.1%) males. The baseline median (IQR) CRF was 10.2 (8.5-12.2), 8.5 (6.9-10.5) and 6.9 (5.7-8.5) METs in the three exercise test categories 1, 2 and 3, respectively. During a median (IQR) follow-up of 5.76 (5.66-5.90) years, 936 participants died, of which 707 (1.4%), 180 (2.4%) and 49 (2.5%) were in category 1, 2 and 3, respectively (**Table 1**).

In analyses adjusted for conventional risk factors and underlying conditions, CRF showed inverse associations with mortality, with more graded associations for category 1 and the overall *fitness cohort* (combined categories 1-3) (**Figure 2**). A doubling of METs was associated with a mortality HR of 0.71 (0.60 to 0.85) in the *fitness cohort.* **Table 2** shows the HRs for all-cause mortality for quintiles of CRF in each risk group. In multivariable adjusted analyses, comparing extreme fifths of CRF the HRs (95% CIs) for mortality were 0.63 (0.52-0.77), 0.54 (0.36-0.82), 0.81 (0.46-1.43) and 0.58 (0.48-0.69) in category 1, 2, 3 and combined groups, respectively (**Table 2**). For category 1 and the overall population, CRF was associated with decreased risk of mortality across all categories of CRF. The association was only evident in individuals in the highest quintile of CRF for category 2.

CRF and mortality risk prediction in the fitness cohort

In the overall population, a 5-year mortality risk prediction model containing established risk factors (age, sex, SBP, smoking, high cholesterol) yielded a C-index of 0.7160 (95% CI: 0.7002 to 0.7319). After addition of CRF measurements to this prognostic model, the C-index increased by 0.0012 (95% CI: -0.0021 to 0.0044; P=.49) (**Supplementary Table S7**). There were no significant C-index changes on addition of CRF to models that included information on underlying conditions (number of medications and prevalent cancer, CVD, or diabetes). Adding CRF to conventional risk factors yielded

an overall NRI of 0.0361 (95% CI: 0.0107 to 0.0615; P=.005) and an overall IDI of 0.0005 (95% CI: 0.0003 to 0.0008; P<.001) for 5-year mortality prediction (**Supplementary Table S8**). The IDI remained consistent on addition of CRF to subsequent models with information on underlying conditions.

Other indices of added value indicated a significant likelihood ratio test (p<0.001), with a modest improvement in prediction when CRF was added to conventional risk factors and underlying conditions in the overall population: the fraction of new information given by CRF was between 2% and 3% (**Supplementary Table S9**). The comparison of 5-year survival probabilities obtained from the models with and without CRF indicates, on overall, similar individual predictions, with estimated probabilities greater than 90% for most participants (**Figure 3**). The difference in predicted survival between the two models, however, varied across levels of risk factors: differences were larger for older participants; in former and active smokers; and in males (**Supplementary Figure S1**).

The role of age, smoking and sex was also evident when estimating 5-year survival across levels of CRF. While for SBP, BMI, and cholesterol the survival was mainly determined by CRF levels, without relevant differences across levels of these three risk factors, conversely the impact of age, smoking and sex (and in part of number of medications) was not negligible (**Supplementary Figure S2**). The estimated 5-year survival was constant for all levels of CRF at 45 years old but closely related to CRF levels at 65 years old; notably, survival was always higher in a 45 years old subject compared to a 65 years old subject at any levels of CRF; this interdependence between CRF and levels of risk factors was also evident for smoking status and sex (**Supplementary Figure S2**). The impact of risk factors on the prognostic relevance of CRF is quantified by the 5-year survival differences across their levels: comparing 20 vs 5 METs, there were 2.9 less deaths per 1000 persons at 45 years old and 12.3 less deaths at 65 years old (**Supplementary Figure S3**). Corresponding values for ranges of other risk factors were: SBP, 8.9 for 170 mmHg and 8.3 for 130 mmHg; BMI, 7.8 for 35 kg/m^2 and 11.2 for 20

kg/m^2; number of medications, 11.7 for 6 and 6.7 for 0; smoking status, 15.8 for current, 9.2 for former, and 6.8 for never smoker; high cholesterol, 7.0 if present and 8.9 if absent; sex, 11.4 for males and 5.8 for females (**Supplementary Figure S3**).

Sensitivity analyses

We performed sensitivity analyses in 51,635 participants from the "*fitness* cohort", without CVD or cancer at baseline (**Supplementary Tables S10** and **S11**). Indices of discrimination and recalibration indicated no improvement in prediction (**Supplementary Tables S12** and **S13**), in line with other indices (**Supplementary Table S14**): likelihood ratio test *P*=.25; fraction of new information given by CRF between 0.5% and 0.7%. Survival analyses indicated, on overall, virtually identical individual 5-year mortality estimated from the models with and without CRF (**Supplementary Figure S4**). The pattern of 5-year survival differences was consistent with the main analysis (larger differences in older participants; former and active smoker; and males; **Supplementary Figure S5**); yet, as survival probabilities were higher (**Supplementary Figure S6**), differences across levels of risk factors were smaller (**Supplementary Figure S7**).

Discussion

In this large-scale, population-based prospective cohort study, we found inverse, independent and graded associations of CRF with all-cause mortality events in a contemporary adult population. Compared to "small risk" and "medium risk" participants, participants in the "minimal risk" group had a reduced risk of mortality across all categories of CRF. Addition of CRF to conventional risk factors improved the overall discrimination of 5-year mortality risk and, more importantly, the predictive value of CRF varied across levels of some relevant risk factors, including age, sex and smoking.

This is one of the first large population-based studies showing that risk prediction can be improved in a pre-screened relatively low risk population by adding information on CRF, estimated on the basis of a submaximal exercise test, to conventional cardiovascular risk factors. CRF is recognized as an important marker of both functional ability and mortality, but it is not routinely assessed in either the general or the specialized clinical setting. Earlier evidence suggests that CRF might add prognostic value beyond established risk factors in predicting mortality risk;[3, 9, 10] however, its value as a clinically useful risk predictor on top of common CVD risk factors has not been confirmed. Using objectively assessed CRF (e.g. exercise capacity by watts) in the current UK Biobank population study, our recent findings provide further insight on the value of assessing exercise tests and whether high-risk patients need additional interventions based on conventional risk factor levels and CRF. Our study shows that CRF provides incremental prognostic value in risk prediction on top of age, sex, SBP, cholesterol and smoking, which are established components of conventional cardiovascular risk scores.[33] Furthermore, the use of CRF assessment in the general population may help in the reclassification of patients into appropriate risk categories more accurately, compared to well-known risk models based on conventional risk factors only, particularly in males older than 60 years and at higher cardiovascular risk (e.g., smoker).

In the study by Celis-Morales and colleagues,[15] which aimed to evaluate whether the association between physical activity and mortality could be moderated by CRF and grip strength, the authors demonstrated independent associations of grip strength and total physical activity with all-cause mortality. In another Biobank study, Kim and colleagues evaluated associations of CRF, grip strength, and their combination with all-cause mortality.[14] Similarly, previous studies have showed an inverse relationship between walking speed, a surrogate biomarker of CRF, and all-cause and cardiovascular death.[34-36] Though some earlier associations are consistent with our current study, we present first time new findings on the associations of CRF with mortality risk across all different pre-determined test

categories from 1 to 3, and primarily focusing on the prognostic value of CRF on the top of commonly used risk factors and its relevance at different levels of cardiovascular risk. Whereas all previous analyses focused on general populations which included a mix of healthy and unhealthy or "high risk" participants, our population was restricted to those at the lowest risk (albeit approximately healthy participants or without pre-existing disease). Moreover, as the survival differences across levels of risk factors and CRF depend on the absolute risk of cardiovascular mortality, the availability of UK Biobank was instrumental in clarifying the prognostic relevance of CRF in a contemporary population, given that the declining rates of cardiovascular death over recent years has positively changed mortality profiles.

Increasing physical activity is the major pathway by which CRF can be increased.[37, 38] Though about half of the variation in CRF is heritable,[39] CRF through physical activity is suggested to exert its protective effects on mortality via beneficial modulation in cardiometabolic risk markers such as blood pressure, lipid and glucose levels, natriuretic peptides, and cardiac troponin T;[40-42]; anti-inflammatory effects;[43, 44] improvement in endothelial function;[45, 46] regulation of cardiac autonomic function;[47] and increase in cardiac output, left ventricular function, oxygen utilization, and the formation of collateral vessels.[42,45,46] Although CRF is a seemingly simple metric, testing an individual's capacity to perform physical work characterizes the ability of multiple physiologic processes to occur synergistically in order to achieve and sustain high levels of PA. Thus, CRF is significantly correlated with measures of pulmonary, cardiovascular, skeletal muscle, and metabolic function. Insufficiencies in one or more systems involved in delivering atmospheric oxygen to the mitochondria of the working organ and/or removal of metabolic by-products from the body reduces [CRF.487]

Our study provides new insights on the beneficial impact of CRF on mortality risk in the general population with a relatively low pre-test risk. Over the last two decades, the scientific literature has witnessed a growing evidence on the beneficial effects of CPX, which has triggered the release of recommendations by several guideline bodies and associations.[48,49] Though enormous strides have been

made in the evidence base, the application of CPX in clinical practice is not well established, especially in general population settings. CRF has not been widely and routinely utilized in clinical practice potentially because of previous technical or resource challenges in its measurement; however, with the introduction of respiratory gas analyzers and automated data processes, it is relatively easy to analyze and compute this measure in real life clinical practice. The current findings suggest that CRF is a mortality risk indicator and provides improvement in the prediction of 5-year mortality especially in those at low cardiovascular risk; indicating that at least in this general population group, it could be a valuable tool to use in clinical practice. In addition, other strengths include the large-scale and well-phenotyped nature of the cohort and comprehensive analysis which employed cutting-edge statistical approaches.

Some limitations should be considered when interpreting the results. The study design was observational and hence causality cannot be inferred.[49] The findings of the UK Biobank cannot be completely generalised to other populations. There may be a possibility of selection bias due to the sample of relative healthy participants who finally accepted in the bicycle exercise tests. Indeed, it has been reported that there is evidence of a "healthy volunteer" selection bias within the UK Biobank sampling population.[50] In addition to other previous results, this study also showed that those participants who reported having cardiovascular disorders and were excluded from the exercise test had a significantly increased risk of death. However, participants were categorized into risk categories based on certain cardiovascular risk and clinical markers which determined the allocation to an individualized, safe bicycle protocol or when exercise testing should be avoided or not needed. Furthermore, potential confounding factors such as concomitant use of specific CVD medications, were not available. At least partly due to strict pre-test exclusions during the baseline examinations, the numbers of fatal cardiovascular event remained low during the 5 years. This was a reason that we could not perform detailed cause-specific mortality analyses. The gold standard measurement for CRF remains the

measurement of peak oxygen consumption (VO2) by CPX using gas exchange analysis,[6] which was not employed by the UK Biobank. However, the Biobank study employed an easily available submaximal testing for CRF assessment, which has good reliability and validity.[1, 2, 21, 22] Submaximal heart rate responses are acceptable and commonly used to assess CRF/METs levels (due to proficiency constraints and the lack of very sophisticated equipment). Additionally, both treadmill and bicycle tests are readily available, useful and reliable ways to define CRF status.[21, 22, 511] It is possible that the study participants were not adequately suitable for risk prediction analyses given the relatively short follow-up time for all-cause mortality outcomes. However, our study findings show that CRF has the potential to be used for 5-year risk prediction in clinical practice. However, its prognostic relevance and clinical meaning could likely be higher for 10 years, although this needs to be demonstrated in future studies. Finally, as with any observational study design, reverse causation bias could have influenced the findings.

Conclusions

Within a contemporary healthy adult UK population, CRF was strongly, inversely, linearly, and independently associated with risk of mortality. Addition of CRF to conventional risk factors improved mortality risk prediction, particularly in subjects at low pre-test risk.

Ethical approval

The UK Biobank research protocol and study design were approved the NHS National Research Ethics Service and all study participants provided written informed consent. Ethical approval was obtained from the North West Centre for Research Ethics Committee (MREC, 11/NW/0382). In Scotland, UK Biobank has approval from the Community Health Index Advisory Group (CHIAG).

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FIGURES

FIGURE 1: 5-year standardized survival by category of bicycle test

Category 1 (cycle rising to 50% level), green; **Category 2** (cycle rising to 35% level), orange; **Category 3** (cycle at constant level), gold; **Category 4** (at-rest measurement), red.
Survival estimates adjusted for age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent cancer, cardiovascular disease, or diabetes at baseline.
Confidence intervals (areas) are shown for Categories 1 and 4.

FIGURE 2: Shape of associations between cardiorespiratory fitness and all-cause mortality, overall and for categories of bicycle test

The left-most estimation (1st fifth) is the reference group (hazard ratio, 1).
Hazard ratios (y-axis) are adjusted for age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent cancer, cardiovascular disease, or diabetes at baseline and plotted against the mean of the natural log transformation cardiorespiratory fitness within each fifth of its distribution (x-axis). Corresponding values are reported in Table 2.

FIGURE 3: Individual Post vs Pre 5-year survival

Pre indicates model with age, sex, systolic blood pressure, body mass index (nonlinear spline), smoking status, high cholesterol, number of medications, and prevalent cancer, cardiovascular disease, or diabetes at baseline.
Post indicates model **Pre** + cardiorespiratory fitness.